

## WE CLAIM:

1. An isolated soluble polypeptide comprising an amino acid sequence of an extracellular domain of an EphB4 protein, wherein the EphB4 polypeptide is a monomer and binds specifically to an Ephrin B2 polypeptide.
- 5 2. The soluble polypeptide of claim 1, comprising a globular domain of an EphB4 protein.
3. The soluble polypeptide of claim 1, comprising a sequence at least 90% identical to residues 1-522 of the amino acid sequence defined by Figure 65.
4. The soluble polypeptide of claim 1, comprising a sequence at least 90% identical to residues 1-412 of the amino acid sequence defined by Figure 65.
- 10 5. The soluble polypeptide of claim 1, comprising a sequence at least 90% identical to residues 1-312 of the amino acid sequence defined by Figure 65.
6. The soluble polypeptide of claim 1, comprising a sequence defined by Figure 1 or 2.
7. The soluble polypeptide of claim 1, wherein the soluble polypeptide inhibits the interaction between Ephrin B2 and EphB4.
- 15 8. The soluble polypeptide of claim 1, wherein the soluble polypeptide inhibits clustering of Ephrin B2 or EphB4.
9. The soluble polypeptide of claim 1, wherein the soluble polypeptide inhibits phosphorylation of Ephrin B2 or EphB4.
10. The soluble polypeptide of claim 1, wherein the soluble polypeptide is a fusion protein.
- 20 11. The soluble polypeptide of claim 1, wherein the soluble polypeptide comprises one or more modified amino acid residues.
12. An isolated soluble polypeptide comprising an amino acid sequence of an extracellular domain of an Ephrin B2 protein, wherein the soluble Ephrin B2 polypeptide is a monomer and binds with high affinity to an EphB4 polypeptide.
- 25 13. The soluble polypeptide of claim 12, comprising residues 1-225 of the amino acid sequence defined by Figure 66.
14. The soluble polypeptide of claim 12, comprising a sequence defined by Figure 3.
15. The soluble polypeptide of claim 12, wherein the soluble polypeptide inhibits the interaction between Ephrin B2 and EphB4.

16. The soluble polypeptide of claim 12, wherein the soluble polypeptide inhibits clustering of Ephrin B2 or EphB4.
17. The soluble polypeptide of claim 12, wherein the soluble polypeptide inhibits phosphorylation of Ephrin B2 or EphB4.
- 5 18. The soluble polypeptide of claim 12, wherein the soluble polypeptide is a fusion protein.
19. The soluble polypeptide of claim 12, wherein the soluble polypeptide comprises one or more modified amino acid residues.
20. A pharmaceutical composition comprising the soluble polypeptide of claim 1, and a pharmaceutically acceptable carrier.
- 10 21. A pharmaceutical composition comprising the soluble polypeptide of claim 12, and a pharmaceutically acceptable carrier.
22. A cosmetic composition comprising the soluble polypeptide of claim 1, and a pharmaceutically acceptable carrier.
23. A cosmetic composition comprising the soluble polypeptide of claim 12, and a pharmaceutically acceptable carrier.
- 15 23. A diagnostic kit comprising the soluble polypeptide of claim 1 and a pharmaceutically acceptable carrier.
24. A diagnostic kit comprising the soluble polypeptide of claim 12 and a carrier.
25. An antagonist antibody selected from the group consisting of:  
20 (a) an antibody which binds to an extracellular domain of an EphB4 protein and inhibits an activity of the EphB4; and  
(b) an antibody which binds to an extracellular domain of an Ephrin B2 protein and inhibits an activity of the Ephrin B2.
26. The antagonist antibody of claim 25, wherein the antagonist antibody inhibits the interaction between Ephrin B2 and EphB4.
- 25 27. The antagonist antibody of claim 25, wherein the antagonist antibody inhibits clustering of Ephrin B2 or EphB4.
28. The antagonist antibody of claim 25, wherein the antagonist antibody inhibits phosphorylation of Ephrin B2 or EphB4.

29. The antagonist antibody of claim 25, wherein the antagonist antibody is a monoclonal antibody.
30. The antagonist antibody of claim 25, wherein the antagonist antibody is a polyclonal antibody.
- 5 31. A pharmaceutical composition comprising the antagonist antibody of claim 25, and a pharmaceutically acceptable carrier.
32. A cosmetic composition comprising the antagonist antibody of claim 25, and a pharmaceutically acceptable carrier.
33. A diagnostic kit comprising the antagonist antibody of claim 25, and a carrier.
- 10 34. A method of inhibiting signaling through Ephrin B2/EphB4 pathway in a cell, comprising contacting the cell with an effective amount of a soluble polypeptide of claim 1.
35. A method of inhibiting signaling through Ephrin B2/EphB4 pathway in a cell, comprising contacting the cell with an effective amount of a soluble polypeptide of claim 12.
36. A method of inhibiting signaling through Ephrin B2/EphB4 pathway in a cell, comprising  
15 contacting the cell with an effective amount of a soluble polypeptide of claim 25.
37. A method of reducing the growth rate of a tumor, comprising administering an amount of a polypeptide agent sufficient to reduce the growth rate of the tumor, wherein the polypeptide agent is selected from the group consisting of:  
  
20 (a) a soluble polypeptide comprising an amino acid sequence of an extracellular domain of an EphB4 protein, wherein the EphB4 polypeptide is a monomer and binds specifically to an Ephrin B2 polypeptide;  
  
(b) a soluble polypeptide comprising an amino acid sequence of an extracellular domain of an Ephrin B2 protein, wherein the soluble Ephrin B2 polypeptide is a monomer and binds with high affinity to an EphB4 polypeptide.  
  
25 (c) an antibody which binds to an extracellular domain of an EphB4 protein and inhibits an activity of the EphB4; and  
  
(d) an antibody which binds to an extracellular domain of an Ephrin B2 protein and inhibits an activity of the Ephrin B2.
38. The method of claim 37, wherein the tumor comprises cells expressing a higher level of  
30 EphB4 and/or EphrinB2 than noncancerous cells of a comparable tissue.

39. A method for treating a patient suffering from a cancer, comprising administering to the patient a polypeptide agent selected from the group consisting of:
  - (a) a soluble polypeptide comprising an amino acid sequence of an extracellular domain of an EphB4 protein, wherein the EphB4 polypeptide is a monomer and binds specifically to an Ephrin B2 polypeptide;
  - (b) a soluble polypeptide comprising an amino acid sequence of an extracellular domain of an Ephrin B2 protein, wherein the soluble Ephrin B2 polypeptide is a monomer and binds with high affinity to an EphB4 polypeptide.
  - (c) an antibody which binds to an extracellular domain of an EphB4 protein and inhibits an activity of the EphB4; and
  - (d) an antibody which binds to an extracellular domain of an Ephrin B2 protein and inhibits an activity of the Ephrin B2.
40. The method of claim 39, wherein the cancer comprises cancer cells expressing EphrinB2 and/or EphB4 at a higher level than noncancerous cells of a comparable tissue.
41. The method of claim 39, wherein the cancer is metastatic cancer.
42. The method of claim 39, wherein the tumor is selected from the group consisting of colon carcinoma, breast tumor, mesothelioma, prostate tumor, squamous cell carcinoma, Kaposi sarcoma, and leukemia.
43. The method of claim 39, wherein the cancer is an angiogenesis-dependent cancer.
44. The method of claim 39, wherein the cancer is an angiogenesis-independent cancer.
45. The method of claim 39, wherein the polypeptide agent inhibits the interaction between Ephrin B2 and EphB4.
46. The method of claim 39, wherein the polypeptide agent inhibits clustering of Ephrin B2 or EphB4.
47. The method of claim 39, wherein the polypeptide agent inhibits phosphorylation of Ephrin B2 or EphB4.
48. The method of claim 39, wherein the polypeptide agent is formulated with a pharmaceutically acceptable carrier.
49. The method of claim 39, further including administering at least one additional anti-cancer chemotherapeutic agent that inhibits cancer cells in an additive or synergistic manner with the polypeptide agent.

50. A method of inhibiting angiogenesis, comprising contacting a cell an amount of a polypeptide agent sufficient to inhibit angiogenesis, wherein the polypeptide agent is selected from the group consisting of:
  - (a) a soluble polypeptide comprising an amino acid sequence of an extracellular domain of an EphB4 protein, wherein the EphB4 polypeptide is a monomer and binds specifically to an Ephrin B2 polypeptide;
  - (b) a soluble polypeptide comprising an amino acid sequence of an extracellular domain of an Ephrin B2 protein, wherein the soluble Ephrin B2 polypeptide is a monomer and binds with high affinity to an EphB4 polypeptide.
  - (c) an antibody which binds to an extracellular domain of an EphB4 protein and inhibits an activity of the EphB4; and
  - (d) an antibody which binds to an extracellular domain of an Ephrin B2 protein and inhibits an activity of the Ephrin B2.
51. The method of claim 50, wherein the cell expresses EphB4 or Ephrin B2.
52. A method for treating a patient suffering from an angiogenesis-associated disease, comprising administering to the patient a polypeptide agent selected from the group consisting of:
  - (a) a soluble polypeptide comprising an amino acid sequence of an extracellular domain of an EphB4 protein, wherein the EphB4 polypeptide is a monomer and binds specifically to an Ephrin B2 polypeptide;
  - (b) a soluble polypeptide comprising an amino acid sequence of an extracellular domain of an Ephrin B2 protein, wherein the soluble Ephrin B2 polypeptide is a monomer and binds with high affinity to an EphB4 polypeptide.
  - (c) an antibody which binds to an extracellular domain of an EphB4 protein and inhibits an activity of the EphB4; and
  - (d) an antibody which binds to an extracellular domain of an Ephrin B2 protein and inhibits an activity of the Ephrin B2.
53. The method of claim 52, wherein the soluble polypeptide is formulated with a pharmaceutically acceptable carrier.
54. The method of claim 52, wherein the angiogenesis-associated disease is selected from the group consisting of angiogenesis-dependent cancer, benign tumors, inflammatory disorders, chronic articular rheumatism and psoriasis, ocular angiogenic diseases, Osler-

Webber Syndrome, myocardial angiogenesis, plaque neovascularization, telangiectasia, hemophiliac joints, angiofibroma, wound granulation, wound healing, telangiectasia psoriasis scleroderma, pyogenic granuloma, coronary collaterals, ischemic limb angiogenesis, rubeosis, arthritis, diabetic neovascularization, fractures, vasculogenesis, and hematopoiesis.

55. The method of claim 52, further including administering at least one additional anti-angiogenesis agent that inhibits angiogenesis in an additive or synergistic manner with the soluble polypeptide.

56. Use of a polypeptide agent in the manufacture of medicament for the treatment of cancer, wherein the polypeptide agent is selected from the group consisting of:

(a) a soluble polypeptide comprising an amino acid sequence of an extracellular domain of an EphB4 protein, wherein the EphB4 polypeptide is a monomer and binds specifically to an Ephrin B2 polypeptide;

(b) a soluble polypeptide comprising an amino acid sequence of an extracellular domain of an Ephrin B2 protein, wherein the soluble Ephrin B2 polypeptide is a monomer and binds with high affinity to an EphB4 polypeptide.

(c) an antibody which binds to an extracellular domain of an EphB4 protein and inhibits an activity of the EphB4; and

(d) an antibody which binds to an extracellular domain of an Ephrin B2 protein and inhibits an activity of the Ephrin B2.

57. Use of a polypeptide agent in the manufacture of medicament for the treatment of an angiogenesis-associated disease, wherein the polypeptide agent is selected from the group consisting of:

(a) a soluble polypeptide comprising an amino acid sequence of an extracellular domain of an EphB4 protein, wherein the EphB4 polypeptide is a monomer and binds specifically to an Ephrin B2 polypeptide;

(b) a soluble polypeptide comprising an amino acid sequence of an extracellular domain of an Ephrin B2 protein, wherein the soluble Ephrin B2 polypeptide is a monomer and binds with high affinity to an EphB4 polypeptide.

(c) an antibody which binds to an extracellular domain of an EphB4 protein and inhibits an activity of the EphB4; and

(d) an antibody which binds to an extracellular domain of an Ephrin B2 protein and inhibits an activity of the Ephrin B2.

58. A method for treating a patient suffering from a cancer, comprising:

(a) identifying in the patient a tumor having a plurality of cancer cells that express EphB4 and/or EphrinB2; and

(b) administering to the patient a polypeptide agent selected from the group consisting of:

(i) a soluble polypeptide comprising an amino acid sequence of an extracellular domain of an EphB4 protein, wherein the EphB4 polypeptide is a monomer and binds specifically to an Ephrin B2 polypeptide;

(ii) a soluble polypeptide comprising an amino acid sequence of an extracellular domain of an Ephrin B2 protein, wherein the soluble Ephrin B2 polypeptide is a monomer and binds with high affinity to an EphB4 polypeptide.

(iii) an antibody which binds to an extracellular domain of an EphB4 protein and inhibits an activity of the EphB4; and

(iv) an antibody which binds to an extracellular domain of an Ephrin B2 protein and inhibits an activity of the Ephrin B2.

59. A method for treating a patient suffering from a cancer, comprising:

(a) identifying in the patient a tumor having a plurality of cancer cells having a gene amplification of the EphB4 and/or EphrinB2 gene; and

(b) administering to the patient a polypeptide agent selected from the group consisting of:

(i) a soluble polypeptide comprising an amino acid sequence of an extracellular domain of an EphB4 protein, wherein the EphB4 polypeptide is a monomer and binds specifically to an Ephrin B2 polypeptide;

(ii) a soluble polypeptide comprising an amino acid sequence of an extracellular domain of an Ephrin B2 protein, wherein the soluble Ephrin B2 polypeptide is a monomer and binds with high affinity to an EphB4 polypeptide.

(iii) an antibody which binds to an extracellular domain of an EphB4 protein and inhibits an activity of the EphB4; and

(iv) an antibody which binds to an extracellular domain of an Ephrin B2 protein and inhibits an activity of the Ephrin B2.

60. A method for identifying a tumor that is suitable for treatment with an EphrinB2 or EphB4 antagonist, the method comprising detecting in the tumor cell one or more of the following characteristics:

- (a) expression of EphB4 protein and/or mRNA;
- 5 (b) expression of EphrinB2 protein and/or mRNA;
- (c) gene amplification of the EphB4 gene; and
- (d) gene amplification of the EphrinB2 gene,

wherein a tumor cell having one or more of characteristics (a)-(d) is suitable for treatment with an EphrinB2 or EphB4 antagonist.

10 61. The method of claim 60, wherein the EphrinB2 or EphB4 antagonist is selected from the group consisting of:

(a) a soluble polypeptide comprising an amino acid sequence of an extracellular domain of an EphB4 protein, wherein the EphB4 polypeptide is a monomer and binds specifically to an Ephrin B2 polypeptide;

15 (b) a soluble polypeptide comprising an amino acid sequence of an extracellular domain of an Ephrin B2 protein, wherein the soluble Ephrin B2 polypeptide is a monomer and binds with high affinity to an EphB4 polypeptide.

(c) an antibody which binds to an extracellular domain of an EphB4 protein and inhibits an activity of the EphB4; and

20 (d) an antibody which binds to an extracellular domain of an Ephrin B2 protein and inhibits an activity of the Ephrin B2.